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ORIGINAL RESEARCH ARTICLE

Potentially harmful drug prescription in elderly patients with heart failure with reduced ejection fraction

Paulino A. Alvarez[1], Yubo Gao[2], Saket Girotra[1], Amgad Mentias[1], Alexandros Briasoulis[1] and Mary S. Vaughan Sarrazin[2]*

[1]*Department of Internal Medicine, Division of Cardiovascular Diseases, University of Iowa Hospitals & Clinics, Iowa City, IA, USA;* [2]*Institute for Clinical and Translational Sciences, University of Iowa, 200 Hawkins Drive, C44-GH, Iowa City, IA 52242, USA*

Abstract

Aims This study aimed to evaluate the prescription frequency of potentially harmful prescription drugs as defined in current heart failure guidelines among elderly patients with a diagnosis of heart failure with reduced ejection fraction and their association with clinical outcomes.

Methods and results We used the Centers for Medicare & Medicaid Services data from a nationally representative 5% sample for the years 2014–2016 to identify patients admitted to acute care hospitals with a primary diagnosis of heart failure with reduced ejection fraction. The primary exposure was filling a prescription for a potentially harmful drug. Potentially harmful drug fills were treated as a time-dependent covariate to examine their association on readmission and mortality. A total of 8993 patients met study criteria. Potentially harmful drugs were prescribed in 1077 (11.9%) patients within 90 days of discharge from the heart failure hospitalization. Non-steroidal anti-inflammatory agents were the most frequently prescribed potentially harmful drug (6.7%) followed by calcium channel blockers (4.7%), thiazolidinedione (0.59%), and select antiarrhythmic (0.33%). Factors independently associated with potentially harmful drug prescription were female gender, Hispanic ethnicity, severe obesity, among others. In the multivariable Cox model, the prescription of a potentially harmful drug was associated with an increased risk of readmission (hazard ratio 1.14; 95% confidence interval 1.05–1.23, $P < 0.001$). Among drug subgroups, only calcium channel blockers were associated with an increased risk of readmission (hazard ratio 1.225; 95% confidence interval 1.085–1.382, $P = 0.0011$).

Conclusions In elderly patients discharged with a primary diagnosis of heart failure with reduced ejection fraction on guideline-directed medical therapy, prescription of a potentially harmful drug was frequent. Calcium channel blockers were associated with an increased risk of readmission.

Keywords Heart failure; Pharmacotherapy; Non-steroidal anti-inflammatory drugs; Pharmacoepidemiology

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**Correspondence to: Mary S. Vaughan Sarrazin, Institute for Clinical and Translational Sciences, University of Iowa, 200 Hawkins Drive, C44-GH, Iowa City, IA 52242, USA. Fax: 319-877-4932. Email: mary-vaughan-sarrazin@uiowa.edu*

Introduction

Heart failure (HF) affects more than 5 million Americans and remains the most frequent reason for hospitalization in patients age 65 or older.[1] Large pragmatic clinical trials have resulted in drug and device therapies that decrease morbidity and mortality in patients with chronic HF with reduced ejection fraction (HFrEF).[2] However, multi-morbidity is present in more than 60% of patients, and 40% of them have five or more co-morbid conditions, increasing the complexity of managing these patients.[3,4] An elderly patient with a diagnosis of HF takes an average of six drugs, meeting the definition of polypharmacy (≥5 medications).[5] Multiple cardiac and non-cardiac drugs with the potential to cause or exacerbate HF or lead to serious adverse events such as arrhythmias or sudden death have been identified.[6]

Since 2005, the American College of Cardiology and American Heart Association HF guidelines have recommended that the following potentially harmful drug (PHD) groups should be avoided in most patients with HF: (i) antiarrhythmic agents, (ii) non-dihydropyridine calcium channel blockers, and (iii) non-steroidal anti-inflammatory agents.[7] In the 2013 update, thiazolidinediones were added to the list of PHDs.[8] All these drug groups share a Class III harm recommendation (treatment may be harmful) with a level of evidence B (results from single randomized trials or non-randomized studies). Information regarding the prevalence of their use among elderly patients with HF and their association in clinical outcomes is scarce.

To address this gap in knowledge, we examined the prevalence of PHD prescription among HFrEF patients and evaluated their association with clinical outcomes.

Methods

Patient population

The study protocol was approved by the institutional review board of the University of Iowa, which waived the need for informed consent. We used Centers for Medicare & Medicaid Services data files from a nationally representative 5% sample, including (i) beneficiary summary file (i.e. enrolment) for years 2013–2016; (ii) Medicare Analysis and Provider Review inpatient files for years 2013–2016; and (iii) pharmacy drug event files (Part D) for years 2014–2016.

We included Medicare patients age 66 years or older who were discharged between April 2014 and September 2016 with a primary diagnosis of HFrEF according to the International Classification of Diseases (ICD) codes (ICD-9 codes: 4280, 42820, 42821, 42822, 42823, 42840, 42841, 42842, and 42843 prior to October 2015; ICD-10 codes: I5020, I5021, I5022, I5023, I5040, I5041, I5042, and I5043 from October 2015 through 2016). We also restricted our cohort to patients who were enrolled in Medicare Part D at the time of discharge to ensure that all prescriptions filled by study participants were identifiable. To further ensure that our study included patients with HFrEF, we restricted the cohort to patients who filled a prescription for an angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB) or angiotensin receptor–neprilysin inhibitor (ARNi), and an HF-specific beta-blocker (metoprolol succinate, bisoprolol, or carvedilol) within 90 days from discharge, as identified in Part D drug fill data. Additionally, we identified the use of loop diuretics within 90 days after discharge for all patients. A sensitivity analysis was conducted on the subset of patients who received loop diuretics.

Patients who were not enrolled in a Part D drug prescription plan had a diagnosis of metastatic cancer or malignant tumour, end-stage renal disease, died during the index hospitalization, or were not discharged home or left against medical advice were excluded. Finally, for each patient, we identified a single 'index' admission, defined as the first admission for HFrEF with no admission during the previous 365 days.

Exposure to potentially harmful drug definition

Patients who filled a prescription within 90 days of discharge for a PHD as defined by 2013 American College of Cardiology/American Heart Association HF guidelines were identified in the Part D prescription file.[8] Specific drugs included non-steroidal anti-inflammatory agents including cyclooxygenase-2 inhibitors (diclofenac, ibuprofen, naproxen, meloxicam, indomethacin, celecoxib, ketorolac, etodolac, nabumetone, diflunisal, fenoprofen, flurbiprofen, ketoprofen, mefenamic oxaprozin, piroxicam, and tolmetin), thiazolidinediones (pioglitazone and rosiglitazone), antiarrhythmics (flecainide and dronedarone), and/or non-dihydropyridine calcium channel blockers (diltiazem and verapamil). In current guidelines, *d*-sotalol, which is no longer available, is categorized as a PHD.[9] We decided not to include racemic sotalol among PHD given that there is no definitive evidence of harm.[6,10]

We evaluated factors associated with a PHD prescription fill within 90 days of discharge. Additional clinical outcomes included all-cause hospital readmission and all-cause mortality. Mortality was defined using the date of death on the Medicare enrolment record. We categorized readmissions diagnosis into the following categories: HF (as previously defined ICD codes), other cardiovascular causes (ICD-9 codes: 390–459; ICD 10 codes: I00–I99), and non-cardiovascular causes.[11]

Patient characteristics were identified from Medicare enrolment data and secondary diagnosis codes on the inpatient discharge record. Age, sex, and race were identified from Medicare enrolment data. Co-morbid diseases defined by Elixhauser *et al*.[12] were identified by ICD-9-CM/ICD-10 diagnoses on the Medicare Provider Analysis and Review hospital discharge record. We also identified additional co-morbidities of importance to HF outcomes, including diabetes mellitus, sleep apnoea, history of major bleeding, history of ischaemic stroke, haemorrhagic stroke, pulmonary embolism or deep vein thrombosis, prior cardiac revascularization, implantable cardioverter defibrillator, or ischaemic heart disease. The co-morbidity score defined by Gagne *et al*. [13] was calculated to assess co-morbid disease burden.

Statistical analysis

Continuous patient characteristics (e.g. age) were reported as mean and standard deviation. Categorical variables were

reported as number and per cent. We used the χ^2 test for categorical variables while one-way analysis of the variance or *t*-test for continuous ones as appropriate to compare demographic variables, co-morbid conditions, prior hospitalization history, and Gagne co-morbidity score between patients who received any vs. no PHD within 90 days after discharge.

We used multivariable time-dependent Cox regression to assess the relative hazard of readmission or death for patients taking a PHD while controlling for other patient characteristics. Patient characteristics were selected for inclusion in Cox models based on the relationship to the outcome, using a statistical criterion of 0.05, and also guided by prior literature and clinical insight. Patients were censored at death, first readmission, or end of follow-up in 31 December 2016. In the multivariable Cox models, the use of a PHD was treated as a time-dependent variable to avoid the potential for survival bias to influence our results (i.e. patients who survive longer may eventually receive a PHD). Specifically, the time-dependent PHD indicator was set to 1 on the day of the first PHD fill and remained 1 for the remainder of the follow-up period. For patients with a prescription of a PHD prior to the HFrEF admission and after discharge, the PHD was assumed to resume immediately upon discharge. For patients with no prior PHD but PHD use after discharge, the PHD indicator was set to 1 on the date of the first PHD fill. For patients with no PHD use after discharge (with or without PHD use prior to the HFrEF admission), the PHD indicator remained 0 throughout the follow-up period. Similar time-dependent variables were defined for separate analyses of each PHD category. Relative hazards were also estimated separately for patients taking non-steroidal anti-inflammatory drugs (NSAIDs), non-dihydropyridine calcium channel blockers, thiazolidinedione, and antiarrhythmics. We used Cox proportional hazard models to evaluate the impact of cumulative PHD use on the risk of death and readmission. In the models, cumulative days of PHD use were treated as a time-dependent variable that accumulated over time with successive PHD refills. Finally, we repeated all analyses on the subset of patients who received loop diuretics prescription within 90 days from discharge of the index hospitalization. The results of the Cox models were reported as hazard ratios (HRs) and 95% confidence intervals (CIs). SAS statistical software (Version 9.4, Cary, NC) was used for analyses, and a *P* value <0.05 was considered statistically significant.

Results

Initially, 42 792 patients with a primary diagnosis of HFrEF on an acute inpatient claim from 1/4/14 through 30/9/16 were identified in the 5% Medicare sample, of which 33 320 were enrolled in Part D during the month of hospitalization. After excluding patients due to discharge disposition, end-stage renal disease, or previous cancer, 26 343 patients remained, of which 11 041 filled a prescription of ACEI/ARB and HF-specific beta-blocker within 90 days of discharge. Finally, we identified the index admission for each patient, defined as the first HFrEF admission over a 365 day period. This left a total of 8993 index admissions for HFrEF in the final cohort (*Figure 1*). Of note, only 150 (1.6%) patients were on an ARNi. The mean time between discharge and death or end of follow-up was 1.25 patient years.

The mean age of the study population was 78.4 years, with slightly more men than women (51.9%). The most frequent cardiovascular co-morbidities were hypertension (85.2%) and diabetes mellitus (48.0%). Almost one-half of the patients had a diagnosis of ischaemic cardiomyopathy or atrial fibrillation. Approximately one-third of patients had a diagnosis of chronic renal failure (*Table 1*).

Potentially harmful drug exposure

There were 1077 (11.9%) patients that filled a prescription for a PHD within 90 days after discharge from the index hospitalization. Non-steroidal anti-inflammatory agents were the most frequently prescribed PHD (6.7%) followed by calcium channel blockers (4.7%), thiazolidinedione (0.59%), and antiarrhythmics (0.33%) (*Table 2*) Only 74 (0.82%) patients filled more than one PHD during that interval. Of those, 682 patients (63.3%) had a prescription of a PHD within 90 days before index hospitalization. Within 1 year of the index hospitalization, 19.4% of the patients had a prescription for a PHD (*Table 2*).

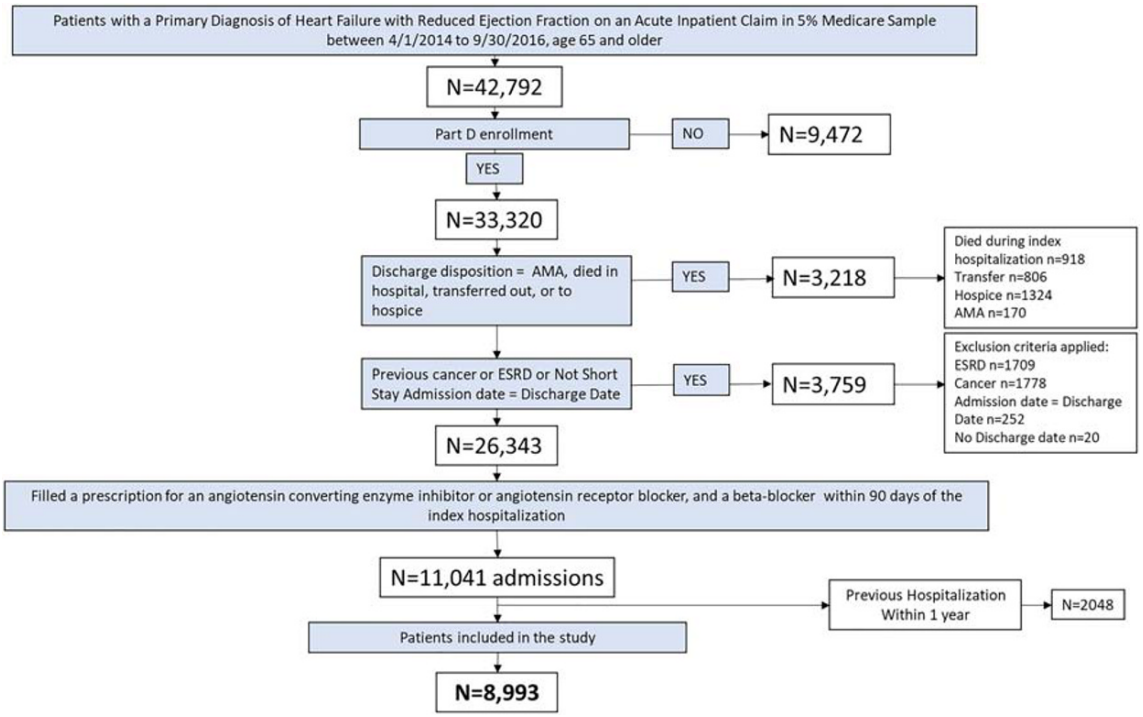
In a multivariable analysis controlling for patient characteristics, pre-admission PHD exposure was the strongest risk factor PHD exposure after HF hospitalization [odds ratio (OR) 14.9; 95% CI 12.9–17.3]; the other factors independently associated with PHD prescription were female gender (OR 1.41; 95% CI 1.24–1.62), Hispanic ethnicity (OR 1.55; 95% CI 1.26–1.90), severe obesity (OR 1.60; 95% CI 1.30–1.96), hypertension (OR 1.37; 95% CI 1.20–1.57), atrial fibrillation (OR 1.48; 95% CI 1.29–1.69), and chronic lung disease (OR 1.46; 95% CI 1.28–1.67). Patients with a history of an implantable cardioverter defibrillator and revascularization were less likely to be prescribed with a PHD. Multivariable predictors of PHD exposure are shown in *Figure 2*. There was no significant difference in the co-morbidity score between patients who were and were not prescribed with a PHD.

Outcomes

Readmission

Overall, 6255 (69.5%) of patients were readmitted after discharge, for an all-cause readmission rate of 1.04 per patient

Figure 1 Flow diagram of the patients included in the study. AMA, against medical advice; ESRD, end-stage renal disease.



year of follow-up (6255/6023 total patient years). The proportion of patients who were readmitted was higher in patients who filled a PHD within 90 days of discharge (73.2%) compared with patients who did not fill a PHD within 90 days (69.1%), for rates per patient year of 1.22 (789/648 total patient years) and 1.02 (5466/5375 total patient years), respectively. In multivariable Cox model analysis that treated PHD initiation as a time-dependent variable, the prescription of a PHD was associated with an increased hazard of readmission (HR 1.147; 95% CI 1.05–1.23, $P < 0.001$). Among individual drug categories, only calcium channel blocker prescription was associated with increased readmission hazard (HR 1.22; 95% CI 1.08–1.38, $P = 0.001$) (*Table 3*). Regarding the causes of readmissions, patients who were exposed to PHD were more likely to be admitted because of cardiac non-HF causes (21.0% vs. 17.9%; $P = 0.0004$) and non-cardiac causes (33.66% vs. 29.27%; $P < 0.001$). There were no statistically significant differences in HF readmission rates between patients who were exposed to PHD and those who were not (17.51% vs. 18.37%; $P = 0.3040$).

Mortality

Overall, 2784 (31%) of patients died during the study period, or 0.25 per patient year of follow-up (2784 deaths/11268 total patient years). In patients who filled a PHD within 90 days of discharge, the proportion who died was 29.2% (315 deaths), compared with 31.2% (2469 deaths) in patients who did not fill a PHD. Death rates per patient year were 0.233 (315/1354 patient years) and 0.249 (2469/7916 patient years) in patients who did vs. did not fill a PHD within 90 days, respectively. In Cox regression models treating PHD use as a time-dependent covariate, PHD use was not associated with mortality (HR 0.96; 95% CI 0.85–1.08, $P = 0.46$) (*Table 3*).

Subgroup analysis

Of the 1077 patients who were exposed to PHDs, 694 (64.4%) had a prescription of a PHD before and after admission and 383 (35.6%) had a prescription of a potentially harmful only after the HF hospitalization. The 90 day readmission rate (43.23% vs. 42.56%, $P = 0.8319$) and 90 day mortality (6.05% vs. 5.48%, $P = 0.7034$) were not statistically different among those groups.

There was no association between PHD use and risk of death with cumulative PHD use <180 days. However, cumulative PHD use of 181–365 days was associated with 0.82 hazard of death (95% CI 0.69–9.97; $P = 0.02$), and cumulative PHD use greater than 365 days was associated with 0.64 hazard of death (95% CI 0.52–0.79; $P < 0.001$), relative to patients who never received PHD. In contrast, PHD cumulative use of 1–90 and 181–365 days and PHD use greater than 365 days were associated with 1.159 (1.070–1256; $P = 0.0003$), 1.32 (1.13–1.53; $P < .001$), and 1.78 (1.46–2.18; $P < 0.001$) hazard of readmission, relative to patients who never received PHD.

We performed an analysis restricted to patients who were prescribed with loop diuretics within 90 days from

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Table 1 Baseline characteristics of the patients included in the study

Variable	All patients (*N* = 8993)	%	Not taking PHD (*N* = 7916)		Taking PHD (*N* = 1077)	%	*P* value
Sex							<0.0001
Female	4313	48.03	3702	46.77	617	57.29	
Male	4674	51.97	4214	53.23	460	42.71	
Race							0.0012
White	6404	71.21	5666	71.58	738	68.52	
Black	1447	16.09	1284	16.22	163	15.13	
Hispanic	850	9.45	714	9.02	136	12.63	
Other	292	3.25	252	3.18	40	3.71	
Age							0.0073
Age 65–74	3293	36.62	2853	36.04	440	40.85	
Age 75–84	3407	37.89	3019	38.14	388	36.03	
Age 85+	2293	25.50	2044	25.82	249	23.12	
Age (mean, SD)	78.39 (8.19)		78.48 (8.18)		77.65 (8.28)		0.0018
Hypertension	7663	85.21	6724	84.94	939	87.19	0.0515
Diabetes mellitus	4317	48.00	3756	47.45	561	52.09	0.0042
Obesity	1475	16.40	1243	15.70	232	21.54	<0.001
Severe obesity	749	8.33	599	7.57	150	13.93	<0.0001
Smoking history	2122	23.60	1884	23.80	238	22.10	0.2173
Sleep apnoea	1093	12.15	943	11.91	150	13.93	0.0576
Chronic renal failure	3062	34.05	2762	34.89	300	27.86	<0.0001
Ischaemic heart disease	3982	44.28	3595	45.41	387	35.93	<0.0001
Valvular heart disease	2928	32.56	2614	33.02	314	29.16	0.0111
Stroke	255	2.84	229	2.89	26	2.41	0.3745
Peripheral vascular disease	1322	14.70	1182	14.93	140	13.00	0.0929
Atrial fibrillation	4158	46.24	3583	45.26	575	53.39	<0.0001
Prior revascularization	2823	31.39	2574	32.52	249	23.12	<0.0001
Pacemaker	1166	12.97	1027	12.97	139	12.91	0.9507
Implantable cardioverter defibrillator	1496	16.64	1382	17.46	114	10.58	<0.0001
Chronic lung disease	3253	36.17	2774	35.04	479	44.48	<0.0001
Gastrointestinal haemorrhage	1950	21.68	1687	21.31	263	24.42	0.0202
Depression	925	10.29	808	10.21	117	10.86	0.5059
Rheumatoid arthritis and other collagen vascular diseases	302	3.36	257	3.25	45	4.18	0.1113
Hypothyroidism	1693	18.83	1489	18.81	204	18.94	0.9175
Previous length of stay	5.83 (10.37)		5.82 (10.47)		5.90 (9.63)		0.8036
Gagne co-morbidity score	4.20 (1.86)		4.21 (1.86)		4.11 (1.86)		0.0908

PHD, potentially harmful drug; SD, standard deviation.

the discharge of the index hospitalization, and we found similar results. For example, the relative hazards of readmission and death were 1.16 (95% CI 1.08–1.26; $P < 0.001$) and 0.95 (95% CI 0.84–1.08; $P = 0.47$) in patients with a PHD relative to patients without a PHD in multivariable Cox regression models (Supporting Information, *Tables S1–S3*).

We identified 2672 patients who were taking beta-blocker and ACEI or ARB or ARNI and spironolactone or eplerenone. Of those, 254 (9.5%) were exposed to PHD. After performing a multivariable analysis, only those exposed to non-dihydropyridine calcium channel blockers had a higher risk of readmission (HR 1.405; 95% CI 1.069–1.848, $P = 0.0003$) (Supporting Information, *Table S5*).

Discussion

We found that 12% of the patients who are discharged from the hospital with a primary diagnosis of HFrEF and treated with a beta-blocker and either ACEI/ARB or ARNi are prescribed with a PHD within 90 days after hospitalization, which increases to nearly 20% by the end of 12 months. Prescription of a PHD is associated with a higher risk of readmission during follow-up, but not higher mortality. Among drug subgroups, only calcium channel blockers were associated with an increased risk of readmission. The main reason for readmission was cardiovascular non-HF conditions. When cumulative PHD exposure was analysed, the use of PHD in the first 6 months after HF hospitalization was not associated with increased risk of death but with increased risk hospitalization if PHD was used within the first 3 months or after 6 months. [14] Possible explanations include an increased burden of non-HF readmissions and unaccounted factors related to HF severity such as left ventricular ejection fraction and functional class in our study.

Pre-admission PHD exposure was the strongest risk factor for PHD exposure after admission with a principal diagnosis of HF with reduced ejection fraction. Further studies are needed to distinguish appropriate inaction from inappropriate clinical inertia.[15]

Table 2 Potentially harmful drugs identified in the study

Drug name	Patients taking drug within 90 days	%	Patients taking drug within 365 days	%
Any potentially harmful drug	1077	11.98	1721	19.14
Non-steroidal anti-inflammatory drugs	610	6.78	1185	13.18
Diclofenac	163	1.81	368	4.09
Meloxicam	151	1.68	260	2.89
Ibuprofen	109	1.21	241	2.68
Naproxen	70	0.78	149	1.66
Celecoxib	61	0.68	100	1.11
Ketorolac	41	0.46	127	1.41
Nabumetone	14	0.16	24	0.27
Indomethacin	12	0.13	24	0.27
Sulindac	7	0.08	13	0.14
Etodolac	5	0.06	8	0.09
Ketoprofen	4	0.04	6	0.07
Piroxicam	4	0.04	6	0.07
Other	5	0.05	16	0.17
Calcium channel blockers	426	4.74	525	5.84
Diltiazem	397	4.41	491	5.46
Verapamil	29	0.32	36	0.40
Thiazolidinedione	53	0.59	72	0.80
Pioglitazone	53	0.59	71	0.79
Rosiglitazone			1	0.01
Antiarrhythmic	30	0.33	41	0.46
Dronedarone	20	0.22	27	0.30
Flecainide	10	0.11	14	0.16

Female gender was an independent risk factor for PHD prescription, and this replicates our observation in a younger cohort of patients.[16] In addition, obesity and diabetes are significant risk factors for the development of HFrEF in women, and these co-morbidities were more frequent in patients exposed to PHD.[17] Hispanic ethnicity has been associated with a lower frequency of ACEI/ARB treatment after hospitalization and non-delivery of complete discharge instructions.[18] In our study that included patients treated with guideline-directed medical therapy, Hispanic ethnicity was associated with increased risk for PHD exposure. Further studies to evaluate the association between PHD medications use and hospital readmission rates are needed.

Non-steroidal anti-inflammatory drugs and non-dihydropyridine calcium channel blockers account for 96% of the PHD identified. Toxic cardiovascular effects of NSAIDs include among others thrombosis, renal impairment with fluid retention, hypertension, and interaction with the therapeutic effect of ACEI and diuretics.[19–24] A meta-analysis that included observational studies and randomized controlled trials of NSAID in arthritis and non-rheumatic diseases showed an increase in the risk of HF exacerbation (relative risk 1.97; 95% CI 1.73–2.25).[25] A retrospective cohort study conducted in Denmark that included patients who survived their first hospitalization for HF showed that one-third of the patients claimed at least one prescription of NSAID at discharge and patients exposed to NSAID had a dose-dependent increased risk of death, myocardial infarction, and hospitalization for HF. The HR (95% CI) for death ranged from 1.22 (1.07–1.39) for diclofenac to 2.08 (1.95–2.21) for naproxen. Of note, this report included patients with primary and secondary diagnosis of HF and was not limited to patients with HFrEF, and although 80% of the patients were treated with loop diuretics, only 27% and

Figure 2 Forest plot of multivariate adjusted risk factors for potentially harmful drug (PHD) prescription. CI, confidence interval.

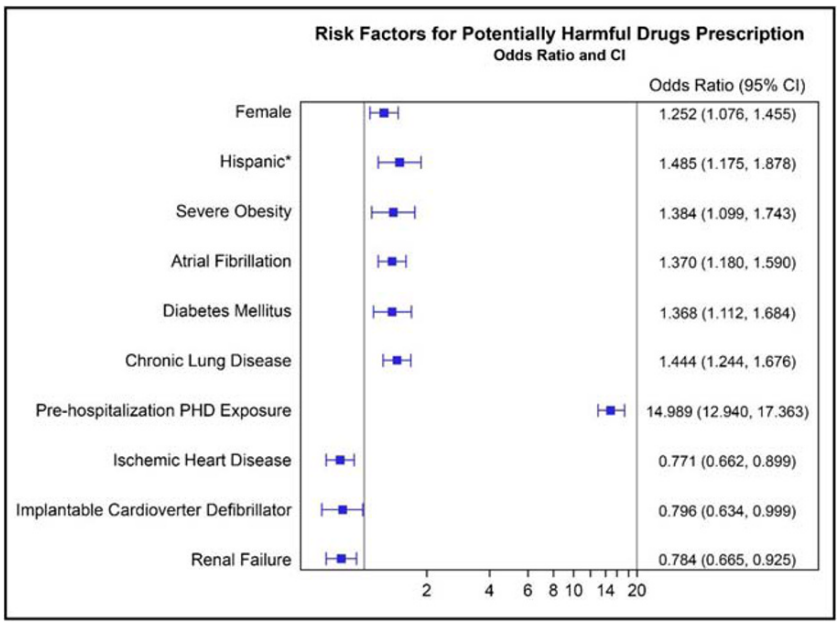

Table 3 Outcomes

	Readmission		Death	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Unadjusted				
Relative hazard, any PHD vs. none	1.157 (1.074–1.247)	0.0001	0.935 (0.831–1.051)	0.2597
NSAID vs. no NSAID	1.080 (0.974–1.197)	0.1449	0.917 (0.786–1.071)	0.2735
Calcium channel vs. none	1.283 (1.139–1.446)	<0.0001	1.125 (0.950–1.333)	0.1730
Thiazolidine vs. none[a]	0.862 (0.620–1.197)	0.3740	0.760 (0.440–1.311)	0.3236
Antiarrhythmic vs. none	0.787 (0.482–1.286)	0.3390	0.257 (0.083–0.797)	0.0186
Risk adjusted				
Relative hazard, any PHD vs. none	1.137 (1.054–1.226)	0.0009	0.956 (0.850–1.076)	0.4573
NSAID vs. no NSAID	1.086 (0.979–1.205)	0.1174	0.983 (0.842–1.148)	0.8304
Calcium channel vs. none	1.225 (1.085–1.382)	0.0011	1.095 (0.922–1.300)	0.3004
Thiazolidine vs. none[a]	0.857 (0.616–1.191)	0.3579	0.850 (0.492–1.470)	0.5617
Antiarrhythmic vs. none	0.755 (0.462–1.235)	0.2631	0.230 (0.074–0.714)	0.0110

CI, confidence interval; HR, hazard ratio; NSAID, non-steroidal anti-inflammatory drug; PHD, potentially harmful drug.
[a]Only patients with diabetes were considered.

44% of the patients were on HF-specific beta-blockers and ACEI or ARB, respectively.[26] Another retrospective cohort study of patients discharged with a diagnosis of HF and prescribed with celecoxib, rofecoxib, or an NSAID show higher risk of death and recurrent congestive HF in patients prescribed with any NSAID or rofecoxib than in those prescribed with celecoxib (HR 1.26, 95% CI 1.00–1.57, and 1.27, 1.09–1.49, respectively). Approximately 50% and 70% of the patients were on beta-blocker and ACEI/ARB respectively and 40% were on calcium channel blockers.[27] The higher risk of HF hospitalization of rofecoxib and NSAIDs (adjusted rate ratio 1.8, 95% CI 1.5–2.2, and 1.4, 1.0–1.9, respectively) was also observed in a large retrospective population-based cohort study.[28] Two randomized controlled clinical trials of NSAID therapy did not exclude patients with a diagnosis of HF who had mild symptoms and had pre-specified criteria to adjudicate HF episodes.[29,30] The overall incidence of HF episodes was low (less than 1%) in both trials.

The data linking non-dihydropyridine calcium blockers with harm were derived from two randomized clinical trials. In the Multicenter Diltiazem Postinfarction Trial, the presence of congestion and reduced ejection fraction (<40%) was associated with a higher rate of a composite primary endpoint of total mortality, cardiovascular mortality, and non-fatal myocardial infarction among patients treated with diltiazem when compared with placebo (HR 1.41; 95% CI 1.01–1.96).[31] In addition, although it was not a pre-specified endpoint, patients treated with diltiazem who had pulmonary congestion at baseline and reduced ejection fraction (EF) were more likely to have CHF during follow-up than those treated with placebo.[32] The evidence of harm was not reproduced in a small trial of patients with idiopathic dilated cardiomyopathy.[33] In the Danish Verapamil Infarction Trial II, there was a significant interaction between HF status and therapeutic efficacy of verapamil. Only patients with no HF exhibit a positive effect of verapamil therapy.[34] This class of medications was consistently associated with increased risk of readmissions across multiple subgroups.

Less than 1% of the patients were exposed to antiarrhythmic and thiazolidinedione. The Cardiac Arrhythmia Suppression Trial showed an increase in mortality in patients who had a myocardial infarction and had asymptomatic or minimally symptomatic premature ventricular beats at a frequency of at least 6 per hour who were treated with encainide or flecainide.[35] Patients hospitalized with new or worsening HF and who had at least one episode of shortness of breath on minimal exertion or at rest (New York Heart Association Functional Class III or IV) or paroxysmal nocturnal dyspnoea within the month before admission treatment with dronedarone were associated with increased early mortality related to the worsening of HF.[36] Evidence from randomized controlled clinical trials has shown an increase in the risk of oedema and HF in patients treated with thiazolidinediones, and this risk is greater with rosiglitazone that pioglitazone.[37,38]

Our findings are in concordance with the results of a nested case–control study conducted in Canada, which included elderly patients with an ambulatory or inpatient HF diagnosis and showed increased readmission rate in patients exposed to PHDs.[39] However, the reported use of guideline-directed medical therapy was low with only 40% and 50% of the patients being prescribed with HF-specific beta-blockers and ACEI/ARB, respectively.

Our study findings should be considered in the context of the following limitations. First, we are unable to account for over-the-counter NSAID prescription. Given that a majority of NSAIDs are not filled with a prescription, the prevalence of NSAID use in our cohort is likely underestimated. Our data can only be applied to NSAID prescribed by a physician. In addition, unaccounted over-the-counter NSAID exposure in patients classified as 'not taking PHDs' could potentially lead to an underestimation of harm of NSAID drugs and a non-significant association with adverse outcomes. Thus, our finding regarding the relationship between NSAID use and outcomes is likely an underrepresentation of the true association of NSAID in patients with HF. Second, we did not

have access to left ventricular ejection fraction data, and we classified patients based on primary ICD codes. To improve the specificity of our cohort, we included only patients who were treated with ACEI/ARB/ARNI and HF-specific beta-blocker. While misclassification is probable due to patients on ARB/ACEI and beta-blocker therapy without HF, our approach has been shown to have an overall specificity ≥95% for the diagnosis of HFrEF and has been used in previous reports.[40–43]

Although the strict inclusion criteria we used facilitate the interpretation of our findings, it has resulted in a relatively small number of patients. This is especially important to consider when interpreting the association of antiarrhythmic and thiazolidinediones in outcomes.

Finally, given the retrospective nature of the study and despite performing a multivariate Cox regression model to adjust for many variables, the risk of unmeasured confounding factors in the analysis of administrative data is unavoidable.

Conclusion

In the current era and in spite of clinical practice guidelines, more than 1 in 10 elderly patients admitted with a primary diagnosis of HFrEF were prescribed with a PHD within 90 days after discharge. This represents a potential area for quality improvement. Calcium channel blockers were the subgroup of PHD associated with increased risk of readmission and education in the pharmacotherapy, and risk of this drug class should be a priority.

Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1: Baseline Characteristics. Sensitivity analysis of patients on loop diuretics.
Table S2: Sensitivity analysis of patients prescribed with loop diuretics.
Table S3: Outcomes (relative hazards: Unadjusted and risk adjusted). Patients on loop diuretics.
Table S4: Cumulative Potentially Harmful Drug (PHD) Exposure.
Table S5: Multivariable Analysis of Patients who were prescribed with an aldosterone antagonist.

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